JPAG
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Laboratories of the Future

Royal Society of Chemistry
Burlington House
Piccadilly
London W1J 0BA

Thursday 11th July 2024

Sponsors of the Joint Pharmaceutical Analysis Group

ROYAL PHARMACEUTICAL SOCIETY

ROYAL SOCIETY OF CHEMISTRY

Event details

The embedding of Industry 4.0 practices within the pharmaceutical industry boosted and accelerated pharmaceutical development: manufacturing, product development and testing have all benefited from the many advancements in the fields of automation, robotics, big data and machine learning. This symposium will feature highlights from industry experts and vendors on trends and case studies showing how industry has adopted (or is considering) new digital and hardware tools to boost efficiency and sustainability in the pharmaceutical laboratories of the future.

Talks will feature a range of topics including:

- Evolution of pharmaceutical processes from industry 1.0 to 4.0
- Virtual reality and artificial intelligence in chemistry laboratories
- Automation of sample preparation
- Predictive modelling of qSAR
- Chemometrics for spectral data analysis
- Chemometrics for metabolomics workflow
- Pharmaceutical forensics

Additionally, we would like to open a call for poster abstracts related to these themes.

Poster submissions are welcome for new or previously presented work and should be submitted by June 20th via events@jpag.org. Abstracts will be reviewed upon submission and authors will be notified by email if their abstract has been accepted or, if revisions are required, feedback will be provided. Authors will be expected to address any feedback / recommendations and conditions of acceptance prior to final submission.

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This letter contains important information which I ask you to read.

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Seating arrangements: Seating is theatre style.

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I hope that you find the day an enjoyable and informative experience.
Lisa Hinchliffe
Chair
JPAG

Programme

09.30 Coffee and registration

09.50 Welcome and introduction to the morning session (Dr Lisa Hinchliffe and Dr Hannah Davies)
10.00 Evolution of pharmacy from 1.0 to 4.0 (Prof Darrin Baines)
10.30 Application of low cost virtual reality and artificial intelligence technology for hand-free cost effective training in laboratories to enhance training and global collaboration (Dr Stephen Hilton)

11.00 Coffee, exhibition, posters

11.20 Journey to Autonomous laboratories (Mrs Pamela Harrison)
11.50 Simplification and automation of retention time prediction workflows (Dr Lucy Morgan)

12.20 Lunch, exhibition, posters

13.25 Introduction to the afternoon session (Mr Valentino Guardascione and Dr Sulaf Assi)
13.30 Chemometrics for spectral data analysis (Prof Tom Fearn)
14.00 Chemometrics for metabolomics workflow (Prof Richard Brereton)

14.30 Coffee, exhibition, posters

14.50 Green laboratories (Miss Sara Martini)
15.20 Pharmaceutical forensics and Data Science- protecting patients with safe and high quality products (Dr Ravi Kalyanaraman)
15.50 Artificial Intelligence-based image reconstruction and image processing for 3D characterisation of vitamin B2 supplements in X-ray Microscopy and Scanning Electron Microscopy with automated phase analyses (Mr Andy Holwell and Dr Ria Mitchell)

16.20 Close

Programme subject to change. Copies of speakers presentations are available to registered delegates on the JPAG website, unless otherwise indicated.

Abstracts

Andy Holwell - ZEISS

Riboflavin alleviates migraine symptoms through the reduction of neuroinflammation. The active is mixed with anti-caking agents, fillers, and lubricants for homogenization and to maximize bioavailability. Multiscale characterization of these supplements provides quality assurance and quantification of the composition, distribution and morphology of components. Two riboflavin supplement capsules presented very different efficacy; in order to understand this, novel 3D characterization techniques were used to characterize them. Nanoscale X-ray microscopy was used to image the powders non-destructively in 3D, and apply advanced machine learning reconstruction approaches to enhance visualization, improve phase contrast, and increase throughput. Automated phase classification quantified components in 3D. Additionally, correlative electron microscopy provided chemical analyses of the formulation. Each capsule's powders exhibited large morphological and structural differences and we identified magnesium stearate binders and calcium phosphate fillers. Thus, non-destructive nanoimaging and AI-based image processing revealed previously unobservable phases. We identified and quantified components not listed as ingredients, demonstrating the capability for quality assurance and regulation of supplements.

Dr Ravi Kalyanaraman - Bristol Myers Squibb

Forensics describes the scientific methods used in an investigation. Pharmaceutical forensics is looking for evidence and using your scientific knowledge and know-how to find proof that will help solve issues in drug manufacturing, patient safety, and crimes. Forensics and Innovative Technologies (FIT) group within commercial quality operations at Bristol-Myers Squibb provides analytical testing to support and solve issues in manufacturing, patient complaints, and to screen suspect and counterfeit products. Several state-of-the-art analytical tools and techniques are used to support pharmaceutical forensics. These include but not limited to Energy Dispersive x-ray Spectroscopy (EDS), Scanning Electron Microscopy (SEM), confocal Raman, portable and benchtop Raman, Infrared (IR), Near Infrared (NIR) micro-spectroscopy, Visible NIR (VNIR) Hyperspectral Imaging (HSI), and Quantum Cascade Laser (QCL) IR spectroscopy. These techniques are used on a regular basis to rapidly screen counterfeit drugs and to identify and characterize particulate and foreign matter in drug product manufacturing. These testing result in a large data set which are often difficult to manage and mine. We have recently introduced web based Spotfire platform and visual data board to better understand the metrics and trending in these investigations. The talk will feature case studies along with the support provided by FIT for commercial products which includes pharma, biologics and cell therapy products and introduce the Spotfire platform.

Prof Darrin Baines - Clarivate

The pharmaceutical landscape stands on the brink of profound transformation as the Fourth Industrial Revolution (4IR) dawns upon us. This presentation delves into the evolutionary journey of pharmacy, tracing its trajectory from the rudimentary frameworks of Industry 1.0 to the sophisticated landscapes of Industry 4.0. As we stand at this precipice of technological advancement, the pivotal question arises: how will 4IR reshape pharmacy practice? Whilst the first three industrial revolutions bestowed pharmacists with a near-monopoly over drug supply, 4IR holds the potential to disrupt this traditional paradigm, ushering in alternative modes of patient treatment and diminishing the conventional roles in medicine supply chains. Embedded within this narrative is the "innovator's dilemma" confronting the pharmacy sector, compelling professionals to reassess their modus operandi. Central to this evolutionary narrative is the imperative for pharmacy to harness emerging technologies such as AI, robotics, IoT, autonomous vehicles, 3-D printing, nanotechnology, biotechnology, materials science, energy storage, and quantum computing. It is through a deep understanding and adept integration of these tools that pharmacists can transcend into the play-masters of tomorrow's medical arena. This presentation serves as a call to action, urging stakeholders to embrace innovation and adaptability as indispensable virtues.

Through proactive engagement with the transformative forces of 4IR, the pharmacy community can fortify its position as a cornerstone of healthcare, ensuring the continued provision of exemplary pharmaceutical care in an ever-evolving landscape.

Prof Richard Brereton - University of Bristol

Metabolomics is the last stage of the central dogma of biology (genomics; transcriptomics; proteomics; metabolomics), the first recorded use of the term being in 2003. The metabolome refers to the complete set of small molecule (<1.5 kDa) metabolites. The workflow consists of 6 main steps : sample collection ; extraction ; instrumental analysis ; data processing / structure elucidation ; chemometrics ; interpretation. Due to the large number of metabolites identified, usually by LCMS, GCMS or NMR, multivariate statistical methods are an essential step in the workflow. There are a large number of software solutions, from ready packaged software to in-house programming and no single package or programming environment is universally accepted. Most metabolomics statistics involves pattern recognition. There is an increasing use of methods for hypothesis tests using resulting in the calculation of p values eg that a metabolite is significant, or a treatment has a significant effect on the metabolome, or that a sample is part of a predefined group. These vary from simple univariate tests such as the t-test or Mann-Whitney U test to multivariate approaches such as PLSDA or statistically based approaches such as ANOVA, and a combination (ASCA).

Prof Tom Fearn - University College London

The use of multivariate analysis, aka chemometrics, to produce quantitative calibrations from spectral data is well established. Used properly, chemometrics is a valuable enabling technology, but it comes with some health warnings. The talk will discuss both sides of the story.

Pamela Harrison - AstraZeneca

AZ’s portfolio expansion, increasing complexity of projects and the need to support accelerations requires our department to increase productivity and agility. We have created a roadmap to transform how we perform laboratory work; dramatically increasing the amount of automation, integrating automated platforms both physically and digitally, generating structured data and then leveraging AI to interrogate the data to ultimately create workflows which can run autonomously.

Phase 1 is fully funded and will focus on evaluating and implementing automation platforms including those used for preparation of samples for analysis. Sample preparation is the one of the most time consuming parts of performing analysis such as LC and has been repeatedly highlighted as an area where repetitive tasks are performed by scientists, therefore the implementation of automation in this area will free up scientists time for more challenging / value adding activities. The progress of these sample preparation platforms will be discussed and productivity, quality and SHE benefits highlighted.

Dr Stephen Hilton - University College London

In recent years, the convergence of emerging technologies has revolutionized scientific research, enabling new possibilities for exploration and discovery. This talk will delve into the captivating realm of blurring boundaries between reality and virtual reality, with a particular focus on the integration of Virtual Reality (VR) and Artificial Intelligence (AI) into scientific laboratories. Traditionally, laboratories have relied on physical experiments and tangible materials. However, the advent of 3D printing presented an exciting opportunity to bridge the gap between the digital and physical realms. My research began by exploring the integration of 3D printing technology into laboratories, revolutionizing prototyping and enabling rapid fabrication of complex scientific equipment. This breakthrough allowed researchers to accelerate their experiments and enhanced their ability to iterate and refine their designs. Building upon the transformative power of 3D printing, my investigations have since ventured into the immersive world of Virtual Reality. VR offers a unique medium to simulate and explore experimental setups and environments that may not be easily accessible or feasible in the physical realm. By harnessing the

potential of VR, scientists can visualize and interact with their experiments in unprecedented ways, transcending the limitations of traditional laboratory setups. This immersive experience not only enhances experimental understanding but also promotes collaborative research and knowledge sharing among geographically dispersed teams. Furthermore, the integration of Artificial Intelligence amplifies the capabilities of VR-driven laboratory environments. AI algorithms can be employed to analyse complex experimental data, enabling real-time insights and facilitating the discovery of meaningful patterns and correlations. Leveraging AI in VR-based laboratories opens doors to intelligent automation, predictive modelling, and augmented decision-making, empowering scientists to extract deeper knowledge and achieve breakthrough discoveries. During this talk, I will present case studies and practical implementations of the integration of VR and AI in my laboratories. By embracing these technologies, researchers can transcend traditional boundaries, accelerating the pace of scientific inquiry and fostering interdisciplinary collaboration.

Sara Martini - AstraZeneca

Laboratories use ten times more energy and four times more water than offices. AstraZeneca is working to reduce these environmental impacts by collaborating with My Green Lab, a global non-for-profit organisations, with the aim of building a culture of sustainability in science. Our efforts have been recognised with two awards in 2023 and as an organisation have saved 5299 kWh/day. We are now leading a number of initiatives towards our commitment to becoming science-based net zero by 2045. The presentation will discuss the continuous improvements of sustainable practices in our laboratories including the storage and management of our cold storages, waste reduction and recycling, and managing plug load amongst others.

Dr Ria Mitchell - Carl Zeiss Microscopy Limited

Riboflavin (vitamin B2) is a water-soluble micronutrient that is essential for the reproduction of cells and growth in the human body, as well as helping to prevent inflammation and ageing. It naturally occurs in a variety of foods including fruit, vegetables and meats, however it is regularly incorporated into vitamin or dietary supplements to bolster healthy lifestyles. Recently, it has been found to potentially be a natural alleviator of migraines due to its preventative effects of migraine symptoms such as neuroinflammation, and now many migraine-relief specific versions of the nutrient exist and can be purchased ‘off the shelf’. However, while most pharmaceutical products are highly regulated, dietary supplements such as these have less stringent regulatory assurances. Here, we have studied two different vitamin B2 supplement capsules from two different manufacturers to characterize and quantify the different components and active phases in 3D. We also apply a variety of novel AI and deep learning reconstruction methods to increase throughput and improve the data generated from 3D imaging, as well as applying 3D phase classification and quantification. We find that these appraoches provide a more holistic interpretation of the samples, imrprove image quality, and allow for faster, more reliable segmentations of phases that are chemically and structurally similar. The results presented here show that non-destructive 3D imaging via X-ray Microscopy (XRM) and associated advanced reconstruction techniques are a useful tool for understanding the composition of pharmaceuticals.

Dr Lucy Morgan - Pfizer

Quantitative Structure-Retention Relationships (QSRR) predictive modelling plays a key role in drug development, aiding in compound identification, retention time prediction, and identification of overlapping peaks. Building a predictive QSRR model has previously been time consuming and prone to human error, with a high associated technical barrier. Here, we have automated large parts of this process and lowered the technical barrier by replacing several software packages, code, and command line tools with a simple web page interface. The processing of experimental data into a refined training set has been significantly simplified for the user, reducing the process from more than an hour to less than 5 minutes. The legacy process used six software packages / interfaces, with the new workflow

reducing this to three. This has also eliminated the possibility of human error in this part of the process.
We have also created a statistically based standard operating procedure for building QSRR models. This includes feature elimination based on compound variability, compound elimination based on modelling performance, and model type screening to determine appropriateness. Our statistical approach for modelling has created standardized and robust models which has helped increase the reliability of our predictive models. Current and future efforts focus on automating hyperparameter optimization for the classifiers used in this modelling process.

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1) Use of multivariate data analysis modelling as an identification test for complex chemical entities

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Objective
Development and validation of a fast and qualitative identification method that covers the complexity of two separate chemical Entities A and B, in order to ensure batch to batch consistency for each, during the manufacturing process.
In principle, a comparison of the spectrum for an unknown sample is carried out against a set of reference spectra via a model. The sample under test is then classed as ‘typical’ or ‘atypical’ based on the model prediction output.

Materials and method
Samples of Entities A and B (230 and 113 batches respectively)

FTIR
Batches ranging across years were analysed by 2 operators using 2 instruments, over 2 days. Different batches were used for development and validation (70/30 ratio respectively). The sample data from the FTIR was subject to multivariate analyses. It was pre-treated and a PCA model was developed and validated for each entity, using Sartorius SIMCA® software.

Results
Model performance characteristics were satisfactory, with R2 & Q2 relatively close to 1: (Table see actual poster)
Specificity and Robustness were also demonstrated for both models. For the former, this was mainly performed via misclassification rates assessment on atypical materials. For the latter, various parameters were assessed using a 6M’s approach. Crystal cleanliness was found to be the main factor to control to avoid false negatives.
Example of model output for Entity A is provided: (see poster)

Conclusion
An analytical method with chemometrics models was developed and validated for both complex chemical Entities A and B, with satisfactory performance for model characteristics as well as specificity and robustness.
Note: only partial lab and chemometric method details provided due to confidentiality.

2) Exploring Pharmaceutical formulation structure using 3D Raman Chemical images

Dr Liam Davison-Gates, Dr Hannah Carruthers, Don Clark, Dr Andrew Ewing, Dr Tina Bonakdar, Dr Fiona Clarke

Chemical imaging has allowed much greater understanding of the distribution of materials within pharmaceutical tablets and guiding the production of high-quality medicines. Currently 2D chemical imaging is the “go-to” method for assessing material distribution in a sample. This method can be limited in determining the true size and shape of material domains within a sample due to the limitations of viewing a 3D object in a 2D space. This issue has been addressed through the collection of 3D chemical images. This is achieved by 2D Raman chemical mapping and iterative sample milling. This allows a full 3D chemical chemical image to be constructed from the 2D slices. These 3D chemical images can be used to assess the distribution of the active pharmaceutical ingredient (API) and excipients in a formulation. This distribution can accurately measure the interconnectivity of chemical domains which may not be possible using 2D imaging. This is important as not every component in a tablet formulation is present as discrete particles. From these 3D chemical images, the contact area, homogeneity, and overall structure of the spatial networks within the formulation can be calculated.

Limitations of this approach are the data acquisition time and inaccuracy of sample transfer and realignment. Long data acquisition times can be due to constant operator intervention steps and the instruments being idle during non-working hours. Inaccuracies in realignment are due to the necessity of reference markers and the offset calculation required after each chemical image. The new parallelised high-throughput approach developed here allows multiple tablets to be milled at once, quick and reliable sample realignment, and Raman map acquisitions to be fully automated. Although, the time to acquire a single 3D chemical image does not change significantly, the benefit of this method is chemical images from multiple samples can be collected in parallel. This method allows an automated workflow that is up to three times faster than the previous method. This method was used to collect a statistically robust data set of 3D chemical images for tablets exhibiting API stability issues. These images showed that the API within the issue batch had smaller particle sizes and thus a greater contact surface area between the API and the excipients.

These developments are being utilised to bring 3D chemical imaging into the pharmaceutical workflow though more efficient data collection. In conclusion, integrating 3D chemical imaging into the pharmaceutical workflow can assist in troubleshooting issues during the tablet manufacturing processes. It provides information about the interactions between different components, which can aid better understanding of tablet stability and performance. The use of automated data collection is a major step in this process.

3) Delivering Digital to Make Chromatographic Analysis more Sustainable - A perspective from within the Pharmaceutical Industry

Matthew Osborne, Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK.

Objective

Chromatographic analysis remains fundamental to controlling the quality of chemical and pharmaceutical materials1. Much of the chemistry, manufacturing and enhanced control strategies have chromatographic analysis at their core to ensure that medicines released are the correct product, the correct dose, and the specified quality. Whilst the optimised chromatographic method is proven to be specific, accurate, precise and sensitive – the burden that chromatography has on the environment is a major contributor to the overall impact that the totality of analytical chemistry practices have2.

The way in which industry 4.0 looks to digitise and structure data provides opportunities to limit and reduce the impact experimental and practical chromatography has on the environment3. For many years, chromatographic method development has been able to exploit data generated from a handful of experiments to generate a separation model based on fundamental chromatographic theory. Software allows the chromatographer to model changing mobile phase & temperature conditions to optimise a

separation on a given stationary phase and solvent system. However, more practical experiments would be needed should the chromatographer find they need to move to a solvent system with a different eluotropic strength or stationary phase to rebuild the model under those conditions. Structuring data collection and processing in a way that allows it to be easily cleaned and organised into large sets is opening opportunities from helping chromatographers predict likely behaviour of component analytes from chemical structures & as a basis of an analytical procedure control strategy facilitating efficient post approval changes to teaching algorithms that can develop chromatographic methods autonomously using machine learning and artificial intelligence. This poster aims to give an overview of how these activities can help our chromatographic labs of the future start driving to a more sustainable chromatographic footprint, through data structure and digitisation with the resultant reduction in the amount of practical experimentation needed and associated decrease in chromatographic waste streams.

1Clarke A, D'Atri V, Fekete S, et al, 2019. Recent Advances in Chromatography for Pharmaceutical Analysis. Anal. Chem. 91, 1, 210–239

2Pena-Pereira F, Tobiszewski M, 2017. The Application of Green Solvents in Separation Processes. Elsevier

3Ghobakhloo, M, 2020. Industry 4.0, digitization, and opportunities for sustainability. Journal of Cleaner Production, 252, 119869.

4)Sustainability in Extractables and Leachables: Implementing Green Chemistry Principles to a HR-LC-MS Screening Method

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Objectives

The objectives of this work are to implement and evaluate green chemistry principles in a high-resolution liquid chromatography-mass spectrometry (HR-LC-MS) screening method for extractables and leachables (E&L), aiming to reduce environmental impact and improve sustainability.

Materials and methods

The study involved redeveloping an HR-LC-MS screening method to substitute acetonitrile with ethanol as the mobile phase. This was evaluated using 21 leachable components purchased from Merck and Waters. The reversed phase method was applied using high-resolution LC-MS with both ESI and APCI ionization techniques. Performance was evaluated on a Waters Acquity I-class UPLC paired with a Synapt G2 mass spectrometer. Comparative analyses of energy input, environmental health and safety (EHS) scores, and chromatographic performance were conducted.1

Results

The updated method conditions led to enhanced separation of a model mixed standard with a reduced run time of 19 minutes compared to 30 minutes for the original method. This change resulted in a 17% reduction in the total use of organic solvent per injection and decreased instrumental energy and gas consumption. Additionally, ethanol was found to be 42% less expensive than acetonitrile, reducing laboratory running costs. The method met all previous acceptance criteria with a suitable limit of detection (LOD) and has been applied for routine analysis in E&L screening studies. The energy input for ethanol production is 50.1 MJ-eq/kg compared to 88.5 MJ-eq/kg for acetonitrile, with overall EHS indicator scores of 2.6 and 4.5, respectively.

Conclusions

The substitution of acetonitrile with ethanol in HR-LC-MS screening methods significantly reduces environmental impact and costs while maintaining analytical performance. Additional research into the use of bioethanol is recommended to further enhance sustainability.

References

1. Capello, C., Fischer, U., & Hungerbühler, K. (2007). A comprehensive framework for the environmental assessment of solvents. Green Chemistry, 9(9), 927–934.

5) DoE Optimisation of Xevo TQ-S StepWave Parameters for LC-MS Analysis of 1,4-Dinitrosopiperazine in a Pharmaceutical Drug Product

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Objectives

The recent discovery of carcinogenic N-nitrosamine impurities in pharmaceutical products present a significant health risk to patients.1 As a result, regulatory agencies around the world have published guidance for allowable limits of N-nitrosamine in pharmaceutical formulations. Pharmaceutical companies must risk assess drug products for the likelihood of N-nitrosamines being present within a drug product, and where a risk is identified an analytical method must be developed to test for the genotoxic impurities.

A major pharmaceutical company requested the development of a Liquid Chromatography - Mass Spectrometry (LC-MS) analytical method for 1,4-Dinitrosopiperazine in a pharmaceutical drug product. Based on an acceptable daily intake of 400 ng/day for 1,4-Dinitrosopiperazine, the sponsor requested a Limit of Quantitation (LOQ) of 26.7 ng/g relative to the drug product's active pharmaceutical ingredient (API).2

This study describes the work performed to optimise the StepWave parameters to increase sensitivity and reach the required LOQ concentration for 1,4-Dinitrosopiperazine in a major pharmaceutical company's drug product.

Method

1,4-Dinitrosopiperazine and deuterated 1,4-Dinitrosopiperazine-d8 reference materials were obtained from LGC Standards. Methanol and formic acid were obtained from Romil. Deionised Water was produced in-house. The finished drug product was supplied by the sponsor. 1,4-Dinitrosopiperazine standards were prepared at a range of concentrations in water for optimisation experiments.

Experiments were performed on an Acquity UPLC coupled to a Sciex 6500+ or a Waters Xevo TQ-S using mobile phases consisting of 0.1% formic acid in water and 0.1% formic acid in methanol and a reverse phase C18 column.

Results

The initial development of this method was performed on an Acquity UPLC coupled to a Sciex 6500+. A combination of poor analyte MS response, poor chromatographic retention on many columns, and incompatibility with common concentration procedures during sample preparation led to an achievable LOQ concentration of 4 ng/mL. This corresponded to 400 ng/g relative to the drug product's API and was too high for the customers' requirements from an analytical method.

During development, the use of a Waters Xevo TQ-S was evaluated. Optimising the MS source parameters is critical for selective and sensitive detection of N-nitrosamines. Manual optimisations were performed and demonstrated comparable performance to the results from the Sciex 6500+.

This instrument contains the StepWave, an ion guide designed to increase ion transmission to the mass analyser by actively removing neutral contaminants. StepWave parameters are often left at default conditions which suit the wide variety of analysis run on these instruments. However, for low molecular weight compounds and more labile species, StepWave parameters can be tuned for more efficient ion transport to the mass analyser.3

Design of Experiments (DoE) was utilised to optimise StepWave parameters and re-optimise the MS source parameters to ensure that each parameter was optimised accurately, simultaneously and in an automated way using a reduced number of injections. Optimising the Xevo TQ-S source and StepWave parameters led to a significant increase in sensitivity for 1,4-Dinitrosopiperazine and resulted in approximately a 15-fold increase in sensitivity. A new LOQ of 0.267 ng/mL was achieved, corresponding to 26.7 ng/g relative to the drug product's API.

This met the sponsors requirements and demonstrated the benefits of evaluating the StepWave for other small N-nitrosamines such as N-nitrosodimethylamine (NDMA) that typically suffer from poor sensitivity by LC-MS. Additionally, there is an increasing industry focus on green and sustainable practices in analytical chemistry.4 Optimising current equipment fully to achieve trace level sensitivity, even for poorly responding N-nitrosamines, is an environmentally friendly and cost effective alternative to purchasing new instruments.

Conclusions

Very low LOQ concentrations are often requested by pharmaceutical companies for N-nitrosamine analysis to meet the regulatory agency guidelines. This study has demonstrated the benefits between considering LCMS systems between different manufacturers. Optimising the StepWave ion guide in a Waters Xevo TQ-S enabled a significant increase in sensitivity for 1,4-Dinitrosopiperazine, and DoE was used to evaluate all parameters simultaneously in an accurate and time effective fashion. As a result of this work, we were able to meet the requested LOQ limits by the sponsor and validate a selective, sensitive and robust analytical method.

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4. Naccarato, A. Development and Application of Green or Sustainable Strategies in Analytical Chemistry. Separations 2023, 10, 32. https://doi.org/10.3390/separations10010032

6) Platform SFC-UV method with adaptable extraction process for GMP analysis of vitamin E in a range of vitamin E supplement matrices

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Objectives

Vitamins are a large group of essential compounds that play an important role in metabolic reactions and cellular processes in the human body. Tocopherols, otherwise known as vitamin E, are fat soluble compounds that can be split into 4 variants: alpha-tocopherol, beta-tocopherol, gamma-tocopherol and delta-tocopherol. A deficiency in vitamin E can cause health problems while an excess intake can lead to

vitamin toxicity or hypervitamintosis.
Vitamin intake depends on diet and can fluctuate depending on diet composition, age, and health issues. Many people therefore take supplements to increase and maintain their intake of vitamins which can come in a variety of forms such as tablets, beverages, and oral sprays. It is important to ensure that products contain the labelled amounts of vitamin E and therefore require quality control assays.
This method describes a platform SFC-UV method for GMP analysis that can be used to determine vitamin E content with a flexible sample extraction workflow to suit the variety of supplement matrices on the market.

Method

Standards containing tocopherols were dissolved in hexane for analysis. Vitamin supplements are extracted into hexane for analysis while products protected by gelatine layers undergo an enzyme digestion and liquid-liquid extraction into hexane prior to analysis. Liquid-liquid extractions are performed on liquid aqueous formulations to transfer the vitamin E into the hexane phase for analysis.
Analysis was performed in 10 mins on an Acquity UPC2 using a Torus 1-AA 3.0 x 100 mm, 1.7 µm column for separation and UV detection at 293 nm.

Results

With a large variety of sample types containing vitamin E, there is no one method capable of extracting them all. Therefore, a range of different extractions are required including “dilute and shoot”, liquid-liquid extraction (LLE), and enzyme treatment. Evaporation and reconstitution can also be used to concentrate samples and enable detection via simple UV based methods and avoid complex mass spectrometry methods. All extraction methods use a final solvent of hexane which is suitable for a single platform SFC-UV method for analysis.
The four forms of tocopherol can be separated effectively using X column by SFC. There are a range of techniques used for the analysis of fat-soluble vitamins such as vitamin E. Reverse phase or normal phase liquid chromatography consume large volumes of organic solvents which can be environmentally unfriendly, toxic and expensive. Gas chromatography presents a risk of thermal degradation of vitamins even when derivation is done prior to analysis. SFC heats and pressurises carbon dioxide beyond its critical point to form a supercritical fluid. In this state, the phase combines the diffusivity and viscosity of a gas phase with the density and solvation power of a liquid phase. SFC presents a sustainable and faster alternative due to its minimal use of organic solvents, higher mass transfer rate and ability to separate compounds of widely different polarities.

Conclusions

A platform method to separate and quantify the four main tocopherol forms using an Acquity UPC2 SFC-UV system and Empower software has been developed for GMP analysis. A range of sample preparation workflows can be used to suit the sample matrix ranging from simple “dilute and shoot” methods to enzyme digestion for complex gelatine encapsulated capsules. This provides a sustainable, efficient and adaptive solution for vitamin E assays on supplement products in a variety of forms.

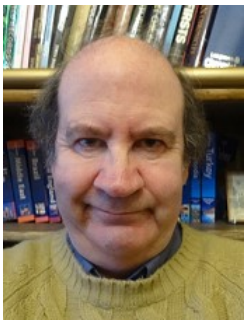
Speaker biographical details

Andy Holwell - ZEISS
Andy Holwell directs the Business Sector Industrial Research at ZEISS Microscopy, encompassing the materials industries for diverse markets from battery materials to pharmaceuticals. After graduating with MChem in Chemistry (University of York, UK), he has gained twenty years' international experience the chemicals, catalysts, fuels, jewellery and metals sectors, in technical, analytical and commercial roles, including ten years with Johnson Matthey in precious metals and chemicals. He currently leads all ZEISS's global strategic marketing, innovation and market education activities for advanced microscopy solutions in the materials industries. He is also a Member of the Royal Society of Chemistry and a Member of the Institute of Materials Minerals and Mining.

Dr Ravi Kalyanaraman - Bristol Myers Squibb
Ravi Kalyanaraman, PhD is the Director of the Forensics and Innovative Technologies (FIT) group within Global Quality Control Analytical Science and Technology at Bristol Myers Squibb (BMS) Company. He received his PhD from the University of Idaho in 1995 and did his post-doctoral work at the University of Puerto Rico. He has been with BMS since 2002 and his work has focused on leading and developing new and novel analytical techniques to detect pharmaceutical counterfeits, and to support particulate and foreign matter characterization in the manufacturing process (bio, pharma, and cell therapy). His interests are mainly in using vibrational spectroscopic techniques, such as Raman, mid- and near-infrared (NIR) and hyperspectral imaging for pharmaceutical counterfeit detection. His group extensively uses microscopy (IR, Raman and SEM) and energy dispersive spectroscopy (EDS) for elemental analysis for particulate and foreign matter investigations. He leads a team in global quality organisation that is involved in the analysis of products received from patient complaints and from corporate security groups and also support Process Analytical Technology (PAT) methods in commercial operation.

Prof Darrin Baines - Clarivate
Professor Baines is a highly regarded health economist, with over two decades of professional experience. He holds a PhD in Economics, an MA in Health Care Ethics, and an MSc in Health Economics, and has published over 100 peer-reviewed papers in international journals. Throughout his career, he has successfully delivered over 150 projects in academia and consulting. He is an expert in pharmacy practice and history. He has published extensively on technology-enabled pharmacy. He is interested in the way in which pharmacy practice has evolved in response to new technology but believes that pharmacists are constrained by the institutions that reimburse and govern the profession. To achieve real beneficial change for patients, new systems for paying and managing pharmacists are required.

Professor Baines is the founding director of Intelligent Parameters Ltd, a consultancy focused on helping companies understand how human and artificial intelligence should be combined.



Prof Richard Brereton - University of Bristol
Professor Richard Brereton took his BA, MA and PhD from the University of Cambridge and is a Fellow of the Royal Statistical Society, Royal Society of Chemistry and Royal Society of Medicine. After a postdoc he was appointed to staff of the University of Bristol, moving to a professor, and now emeritus. He has published 9 books, over 400 articles, and has given over 150 invited lectures in 30 countries. His work has been cited over 15,000 times (Google scholar). He is Editor-in-Chief of the journal Heritage Science, columnist for Journal of Chemometrics and a member of several editorial boards. His latest book Data Analysis and Chemometrics for Metabolomics is in preparation with Wiley.

Prof Tom Fearn - University College London
Tom Fearn is Emeritus Professor of Statistical Science at University College London, UK. Before joining UCL in 1989 he worked for the Flour Milling and Baking Research Association (FMBRA) at Chorleywood, where he first began to calibrate NIR instruments (a 6-filter InfraAlyser 2.5) in 1978. His interest in NIR and in chemometrics more generally has continued to the present. He received the Tomas Hirschfeld award for contributions to near infrared spectroscopy in 2001, and is past President of the International Council for Near Infrared Spectroscopy.

Pamela Harrison - AstraZeneca
I have been at AstraZeneca for 16 years. In that time I have worked within product development, and have been heavily involved in bringing automation to the department. This automation journey started with a stability system for storing predictive stability samples but more recently I have been focusing on sample preparation and a number of solutions to increase our use of automation in this area. My spare time is mostly spent with my 2 daughters but I also love to wild swim, paddle board (even though I'm not very good at it!) or craft.

Dr Stephen Hilton - University College London
Dr Stephen Hilton is an Associate Professor at UCL School of Pharmacy. Dr Hilton's diverse research interests range from medicinal chemistry, scale-up synthesis and new technology with an emphasis on the applications of 3D printing and Virtual Reality in Synthetic Chemistry and Pharmaceutical applications. Dr Stephen Hilton is the Inventor of the IKA FLOW - continuous flow reactor, which is partnered and sold by IKA and was developed during the pandemic using 3D printing and Virtual Reality Software. The IKA FLOW features unique 3D printed reactors at its core that were developed in the Hilton group and the group’s current focus is on the application of 3D printing towards new continuous flow technology, catalysis, methodology and linking of the technology to Virtual Reality and inclusion of AI. Dr Hilton has pioneered the development of VR linked to AI in education and this has featured recently in Nature and Metaconnect 2023.

Sara Martini - AstraZeneca
Analytical Industrial Placement student undertaking a Master's degree in Chemistry from the University of Edinburgh.

Dr Ria Mitchell - Carl Zeiss Microscopy Limited
Dr Ria Mitchell is an Applications Development Engineer in raw materials Industrial Research at Carl Zeiss Microscopy in the UK. While she has a background in Earth Sciences, her practical knowledge of microscopy, particularly 3D microscopy, has enabled her to develop interdisciplinary skills and interests across a range of subject areas and areas of microscopy, especially in multi-scale and multi-dimensional correlative imaging. Ria completed her PhD at Royal Holloway, University of London, before undertaking postdocs at The Natural History Museum in London and Swansea University. She then undertook an Experimental Officer role at the University of Sheffield running the Zeiss Versa 620 X-ray Microscope (XRM), before beginning her role with Zeiss.

Dr Lucy Morgan - Pfizer

Dr. Lucy Morgan is a Senior scientist in Chemical Analytics within the Analytical Research and Development department at Pfizer Inc. and is also a co-chair for CAMS in the data science line. Dr. Morgan's research interests lie at the interface of laboratory experiments, computer modelling, and data science. Part of her role at Pfizer involves innovating current procedures and practices in the aim to automate repetitive tasks, use smarter tools for handling data and procedures, and streamline workflows.

Dr. Morgan began her career at the University of Kent, Canterbury, studying Forensic Science at the undergraduate and master's level, before receiving her Ph.D. in Chemistry on the topic of mechanical and catalytic properties of ceria. She then joined the Faraday Institution, working as a post-doctoral researcher at the University of Bath for 3 years, researching molecular dynamic modelling of battery materials. Dr. Morgan joined Pfizer in late 2021 and has since worked as a data scientist and analytical chemist.

In her spare time Dr. Morgan enjoys the challenges of escape rooms, swimming, and a very novice attempt at crazy golf.

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Monday 18th May 2026
The Chromatographic (Analytical) method life cycle (2026): From cradle to grave (III)/ ChromSoc Spring Symposium - Day 1
Royal Society of Chemistry, London
We are delighted to invite you to the Spring Symposium 2026 on The Chromatographic (Analytical) method life cycle (2026): From cradle to grave (III), co-organised by ChromSoc and JPAG. This exciting event will take place on 18-19th May 2026 at RSC Burlington House, London, UK.
Like previous meetings, it will have a full and exciting topic and speakers program one that has also been purposefully designed to facilitate delegate and exhibitor access to a wide range of scientists, many of whom are leaders in their field.

Register now at www.jpag.org/cp197

Tuesday 19th May 2026
The Chromatographic (Analytical) method life cycle (2026): From cradle to grave (III)/ ChromSoc Spring Symposium - Day 2
Royal Society of Chemistry, London
We are delighted to invite you to the Spring Symposium 2026 on The Chromatographic (Analytical) method life cycle (2026): From cradle to grave (III), co-organised by ChromSoc and JPAG. This exciting event will take place on 18-19th May 2026 at RSC Burlington House, London, UK.
Like previous meetings, it will have a full and exciting topic and speakers program one that has also been purposefully designed to facilitate delegate and exhibitor access to a wide range of scientists, many of whom are leaders in their field.

Register now at www.jpag.org/cp192

Interested in any of these meetings?
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